Veterans Affairs Medical Center
Durham, North Carolina

Duke University
Medical Center

Research Update

Institute for Clinical and Epidemiological Research

Volume VII, No. 1 | A Veterans Affairs Center of Excellence | Spring 2004

ALS National Registry Update

The National Registry of Veterans with Amyotrophic Lateral Sclerosis (ALS), a nationwide record of living veterans with ALS developed by the Durham VA Medical Center with cooperation of the Lexington (Kentucky) VA Medical Center, has reached its first-year anniversary. The registry's primary goals are to identify and enroll all veterans with a verified diagnosis of ALS, collect interview data and blood samples for DNA banking, and follow these veterans throughout the course of their disease. Prior to the registry's formation, there was no mechanism in place to definitely ascertain cases of this disease among veterans or track those individuals over time. It is hoped that the registry will give VA researchers, and medical researchers nation-wide, an understanding of the natural history of ALS as well as important epidemiological data on veterans with ALS. In addition, the registry will be a source for recruiting these veterans into clinical drug trials or other studies that may improve health or quality of life outcomes.

"We've had great success assembling a team to process the veterans who are calling in, as well as conducting systematic assessments of VA electronic medical records to find veterans who may not have known about the registry and offering them an opportunity to be signed up," says Eugene Oddone, M.D., co-principal investigator of the study.

The registry's main activity of enrolling patients began in April 2003 and is overseen by Kelli Dominick, Ph.D., acting epidemiologist for the project. "We identify patients in two ways," says Dr. Dominick. "The first is through the VA medical record databases. When we find a record with a patient with a diagnosis for ALS, or a related disease, we contact that person and ask if they would like to be added to the registry. There are approximately 2800 veterans with this diagnosis in VA medical records, so it takes a lot of time to call and screen them. The other way we recruit veterans, especially those outside the VA system, is through Websites, clinics, physician referrals, and the ALS Association. We publicize the registry and hope that veterans will call us to participate. There are 30 to 40 ALS clinics throughout the country, and we're working with them to help us recruit veterans who aren't enrolled in the VA healthcare system. Our goal is to enroll all veterans with ALS who are interested in participating. Right now, we have about 580 patients who have consented to participate in the registry. Of these, we've reviewed the medical records of about 300 who are now enrolled. We are in the process of obtaining and reviewing the medical records of the rest."

To be certain of an ALS diagnosis, the registry seeks copies of all the patient's medical records and then has one of six neurologists experienced in ALS diagnosis review the patient records. These neurologists are located at the Durham, Lexington, and the Cincinnati VA Medical Centers.

Medical record verification by the neurologists is being overseen by Edward J. Kasarskis, Jr., M.D., Ph.D., co-principal investigator of the study. Dr. Kasarskis is chief of Neurology Services at the Lexington VA Medical Center and has had extensive experience in ALS research. His clinical research currently focuses on the nutritional needs and support of ALS patients, and he has served on an advisory group under the auspices of the American Academy of Neurology to develop practice guidelines for the care of ALS patients in regard to their nutritional care.

"With thousands of cases that we'll have to examine, there's no way we can personally

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examine these patients," says Dr. Kasarskis. "There is no simple blood test because a simple blood test hasn't been invented. ALS is very much a clinical diagnosis, so the only way we can really know before death is by examining the medical records. There are international medical community criteria, known as the El Escorial World Federation of Neurology criteria for the diagnosis of ALS. Once it is determined by a patient's record that he or she has ALS, based on these criteria, then that patient will be admitted to the registry."

Dr. Kasarskis sees part of the registry's worth in its long-term value. "I think the registry is going to serve as a platform for many future studies. Its value will be in the mass of clinical data that are being accumulated – data on survival, data on medications that ALS patients are taking, and data on rates of progression. We'll be looking at age, racial, ethnic and geographic backgrounds as well. And out of this clinical repository we will be able to start examining gene environment interactions or specific predisposing or modifying genes that might be associated, for instance, with a rapid course, or a slow course, a young onset of the disease, or an older age onset. Those factors are presumed to have a genetic component. So our registry activities are building on that component with the anticipation that, in the future, we will have quite a bit of research activity around participants in this registry."

"Another value of the registry," says Dr. Kasarskis, "is a theoretical one. If someone three years from now discovers a new gene that is strongly linked to ALS, they will be able to make a request to obtain DNA specimens. This researcher might be able to immediately acquire 500 samples of DNA from 500 patients that are already clinically characterized, something that an investigator would not be able to do on his or her own. ALS is a fairly rare disease, and having opportunities to have DNA samples on a large number of cases would be impossible to acquire without the storage of a large number of DNA samples from persons already screened for ALS."

"One of the main goals of the registry is to allow VA and non-VA researchers access to the registry's data," says Dr. Oddone, "as well as inform registry members of any study we think has merit. The registry has a scientific review committee that will help determine the protocols we should have in place to judge the scientific merit of any studies by outside investigators who want access to the registry."

The scientific review committee will review all studies, including clinical trials and epidemiological investigations, that seek access to registry data. This committee is made up of 11 nation-wide scientists who have expertise in ALS, DNA storage, or blood banking, and represent such organizations as the national ALS Association, the Department of Veterans Affairs, the National Institute of Environmental Health Studies, the National Institute of Neurological Disorders and Stroke, and Harvard University.

So far four research teams have requested use of registry data for ALS projects which will examine 1) gene and environmental interactions in ALS; 2) ALS biomarkers in Gulf War veterans; 3) metabolic profiles and signatures in ALS; and 4) the prevalence of ALS in five Illinois counties.

"The exciting thing about the registry for the scientific community," says Dr. Oddone, "is the opportunity to do gene and environment studies on a large enough population of patients with ALS to be able to tease out some causation. This registry will provide us with data that we hope will push ALS research forward in an important way."

The ALS Registry's funding by the Cooperative Studies Program is $1.4 million for three years. For more information send a message to als@med.va.gov.

Sheri Keitz Wins Duke Teaching Award

Sheri Keitz, M.D., Ph.D., is one of three first-time winners of the Duke University School of Medicine's new Master Clinician Teaching Award. The award was granted this past February. Dr. Keitz is the associate chief of staff for education and director of the PRIME program, which provides training in primary care for medical residents for the Durham VA Medical Center, an assistant professor of general internal medicine at Duke University Department of Medicine, and director of Duke's Managed Care Learning Center.

The award is designed to "honor individuals with superlative accomplishment and service in the areas of clinical care and teaching" and recognizes "clinical practitioners who exemplify the highest standards of clinical care, pedagogy, and professionalism." Candidates are nominated from the faculty, house staff, and student body. The award committee considers an individual's past and future contributions to medical student education. The award carries a $15,000 annual prize for two years and is non-renewable.

"Teaching is an incredible amplification of the impact you can have on one patient," said Dr. Keitz. "If I take care of one patient and assist him that day, that is very gratifying. But as a teacher, you can extend that far beyond one patient and impact distant places in the future."

In the nominating process, Dr. Keitz was noted for her "enormous enthusiasm" and finding "creative ways to make teaching points, and always goes the extra mile to create relevant teaching experiences." She was also noted for "her single-minded commitment to innovation and leadership in medical education on Duke's campus."

Adapted, in part, from the February 23, 2004 INSIDE, a newsletter for employees of Duke University Medical Center and Health System.

Stacey Kovac Begins Career Development Award

Stacey H. Kovac, Ph.D., formerly a clinical research psychologist with the Deep South Center on Effectiveness at the Birmingham VAMC and an assistant professor of medicine at the University of Alabama at Birmingham (UAB), has been granted a three-year Research Career Development Award. She applied for and received the award through the Birmingham VAMC and then transferred to the Durham area. Dr. Kovac will also have an appointment as an assistant research professor at Duke University's Department of Medicine, Division of Internal Medicine.

Dr. Kovac received a B.A. in psychology from West Virginia University in 1996. She received her M.A. in clinical psychology in 1998 and received her Ph.D. in clinical psychology in 2001, both from the University of Southern Mississippi. She completed a postdoctoral fellowship with the Center for Outcomes and Effectiveness Research and Education at UAB. She is a licensed clinical psychologist in Alabama with extensive experience in patient focused behavioral interventions.

While at UAB and the Birmingham VAMC, Dr. Kovac aided investigators with patient instrument selection for measurement of health related quality of life, functional status, symptom assessment, and patient satisfaction, as well as helped design and implement patient-based outcomes assessment protocols, and provided psychometrics and measurement theory analysis and interpretation of health outcomes data. Dr. Kovac was also an active investigator with the UAB Center for Education and Research Therapeutics in musculoskeletal disorders where she served as the center's psychometrician for studies involving non-steroidal anti-inflammatory medication safety and glucorticoid-induced osteoporosis, and additionally provided expertise on theories related to behavior change.

For her Career Development Award, Dr. Kovac plans to apply her behavioral science background to interventions targeted to improve the process of health care delivery and provider performance. "Many existing improvement interventions are targeted at changing provider behavior and use some behavioral science," says Dr. Kovac, "but behavioral modification principles, such as shaping or prompting behaviors, are rarely meshed explicitly into research designs. My long-term goal is to integrate behavioral modification principles and quality improvement methodology in order to develop and implement health care improvement initiatives across many disease states within the VA health system."

"Specifically," says Dr. Kovac, "I plan to address patient safety in the use of non-steroidal anti-inflammatory drugs (NSAIDs). Both prescription and over-the-counter (OTC) NSAIDs have the potential to cause serious patient safety risks, especially when used incorrectly. I plan to identify current NSAIDs patient safety problems within the Durham VA Medical Center through patient medical records and patient survey data. I want to evaluate the dual use of OTC and prescription NSAIDs and the potentially harmful interactions of a prescribed NSAID with another prescribed medication, such as corticosteroids and anticoagulants. I will then compare the Durham VA results to nationwide samples of VA patients. From there, I will develop an NSAID patient safety pilot project to test the feasibility of a provider-level intervention on NSAID patient safety. At the end I would like to develop a VA independent investigator initiated randomized-controlled trial integrating behavioral modification principles and improvement methodology on NSAID patient safety at the provider level."

During her Career Development Award, Dr. Kovac will also be seeing patients as a clinical psychologist in Durham VAMC Psychology Services.

"The VA system is an ideal setting for merging behavioral modification principles and health care improvement," says Dr. Kovac. "The VA databases, such as the Computerized Patient Record System, will allow me to obtain data quickly on provider practice patterns, which can be fed back to providers in order to attempt to improve practice pattern behavior. The multidisciplinary nature of the Durham center, the array of disciplines of the faculty, and the variety of research projects funded offer opportunities to explore a number of future projects."

Dr. Kovac is a member of Academy Health, the American Psychological Association, the Association for Rheumatology Health Professionals, and the Society for Behavioral Medicine.

Her mentors will be Morris Weinberger, Ph.D., and Eugene Oddone, M.D., M.H.Sc.

Low-Carbohydrate versus Low-Fat Diet Study

In a recent study, published in the May 18 issue of Annals of Internal Medicine*, researchers Will Yancy, M.D., M.H.S., Maren Olsen, Ph.D., both of the Durham VA Center of Excellence in Primary Care, and John Guyton, M.D., Ronna Bakst, R.D., and Eric Westman, M.D., M.H.S., of Duke University Medical Center, found that "a low-carbohydrate diet program led to greater weight loss, reduction in serum triglyceride level, and increase in HDL cholesterol level compared with a low-fat diet." Though a low-carbohydrate diet has gained widespread public attention, until recently it had only modest scientific support from studies of short duration.

One of the significant differences in this study compared

to others is the adherence to the Atkins weight loss approach. "The low-carbohydrate diet intervention in our study was modeled after the Atkins diet approach that was practiced in the Dr. Atkins' clinic," says Dr. Yancy, lead researcher in the study. "The low-carbohydrate diet group received diet counseling and nutritional supplements, similar to what Dr. Atkins' actual patients received."

The researchers recruited 120 overweight, hyperlipidemic volunteers from the Durham VA outpatient clinic who were randomly assigned to follow, over a 24-week period, a low-carbohydrate, ketogenic diet or a low-fat, low-cholesterol, reduced-calorie diet commonly used to induce weight loss and decrease serum lipid levels. Low-carbohydrate diet participants were instructed to initially restrict their carbohydrate intake to less than 20 grams per day with unlimited consumption of meat, fowl, fish or shellfish, unlimited eggs, and more limited amounts of cheese, salad vegetables, and low-carbohydrate vegetables. Low-fat diet participants were instructed to less than 30% daily intake from fat, less than 10% intake of saturated fat, and less than 300 mg cholesterol daily. In addition, this group was counseled to restrict calories – about 500 calories less than would be needed to maintain their weight.

At the end of 24 weeks, the low-carbohydrate diet group had greater weight loss than the low-fat group, 26 pounds versus 14 pounds. Both groups lost predominantly fat mass over this 24 week period, with the percentage of total weight loss due to loss of fat being similar in both groups. The low-carbohydrate diet group lost a greater amount of water in the first two weeks than did the low-fat diet group, supporting anecdotal reports of diuresis with the low-carbohydrate diet, though water loss was similar between the groups after two weeks.

The biggest concern about the low-carbohydrate diet is that increases in fat intake might have detrimental effects on serum lipid levels. Surprisingly, the low-carbohydrate diet group experienced a greater decrease in serum triglycerides and a greater increase in HDL (good) cholesterol, compared with the low-fat diet group. Meanwhile, the LDL (bad) cholesterol changes were similar in both diet groups. While the average change in LDL cholesterol implies that the diet is safe, it is important to note that 30% of the low-carbohydrate diet recipients experienced an increase in LDL cholesterol of at least 10% from baseline. The study recommends that serum lipid profiles of followers of this low carbohydrate diet be monitored.

*Yancy Jr. WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. "A Low-Carbohydrate, Ketogenic Diet versus a Low-Fat Diet to Treat Obesity and Hyperlipidemia" *Annals of Internal Medicine* 2004 (May 18); 140(10): 769-777.

Children and Parental Obesity

In a recent study researchers found "an association between the number of children and obesity among both middle-aged men and women after adjustment for other predictors of obesity." Published in the January issue of the *Journal of Women's Health**, researchers Haoling Weng, M.D., M.H.S., and Lori Bastian, M.D., M.P.H., both of the Durham VA Center of Excellence in Primary Care and Duke University's Department of Medicine, Donald Taylor, Jr., Ph.D., of Duke University's Terry Sanford Institute of Public Policy, Barry Moser, Ph.D., of the Duke Comprehensive Cancer Center, and Truls Ostbye, M.D., Ph.D., of the Duke Comprehensive Cancer Center and the Duke University Medical Center, concluded that the study "suggests that a substantial portion of the effect of obesity related to parenthood has to be social, cultural, or psychological, as it is difficult to imagine a physiological mechanism through which men could gain weight during pregnancy or after childbirth."

"This is the first study to both examine the association of the number of children on the prevalence of obesity among middle-aged couples," states the authors, "and to demonstrate increasing rates of obesity in both men and women with increasing numbers of children."

The study also found that women who had high pre-conceptual weight, had excessive gestational weight gain, are African American, and attained lower levels of education were most vulnerable in retaining significantly more weight, as were men with lower education or lower socio-economic status.

Though physiological factors have long been suspected of playing a role of weight gain in the mother, behavioral mechanisms most likely contribute to weight gain in both the mother and father. Increased food intake and/or reduced physical activity could be contributing behavioral factors, as well as increased parental responsibilities leave less time to focus on health behaviors that promote weight loss and/or physical fitness. This points to a need for family-based behavioral interventions and future studies examining changes in, and attitudes toward, diet, physical activity, and exercise among couples with small children.

Drs. Ostbye and Bastian are currently working on a weight-loss intervention trial funded by the National Institute of Diabetes & Digestive & Kidney Diseases on overweight women post-partum that was developed based on the results of this study.

*Weng HH, Bastian LA, Taylor DH, Moser BK, Ostbye T. "Number of Children Associated with Obesity in Middle-Aged Women and Men: Results from the Health and Retirement Study" *Journal of Women's Health* 2003 (Jan.); 13(1): 85-91.

Blood Pressure Improvement Among Functionally Illiterate Study to Begin

Elevated blood pressure, a major risk factor for stroke, coronary artery disease and congestive heart failure, is adequately controlled for only a third of all patients with hypertension. Functional illiteracy, particularly among the elderly, likely contributes to this poor level of blood pressure control. Research suggests poorer hypertension knowledge, poorer overall health status, and increased blood pressure are all related to functional illiteracy.

A new two-year study by Hayden Bosworth, Ph.D., Eugene Oddone, M.D., and Maren Olsen, Ph.D., proposes a randomized, controlled trial "to tailor a health communication intervention to improve functionally health illiterate (FHI) patients' management of their hypertension, and to evaluate the impact of this intervention on health outcomes."

The researchers will randomize 250 hypertensive FHI patients, recruited from primary care clinics, into an intervention group and a usual care group. The intervention group will receive telephone communication bi-monthly from a nurse, tailored to individual needs through an initial needs assessment, and to promote medication adherence and improved health behaviors such as diet and exercise. They will also receive visual aids to encourage understanding and adherence to medical regimens as well encouragement of support from the patient's family or close friends to help insure patient adherence. The usual care group will receive no contact by the nurse and will only be contacted at the six months and 12 months post baseline evaluation in order to complete the same outcome measures as the other groups. The care for this group will not change.

The intervention's impact will be assessed during any patient clinic visit over a 12-month period, as well as an evaluation of changes in patient hypertension risk perception, the patients' confidence level in following the recommended regimen, self-reported adherence to the regimen, and satisfaction with care at the six and 12 month period.

"We expect that the intervention will improve patient's management of their hypertension," says Dr. Bosworth, "and demonstrate an effective, and cost-efficient, method for clearly conveying health information to adults with low health literacy to improve their blood pressure control and reduce their risk of cardiovascular disease. If successful, our intervention will constitute an important health communication tool that can improve the lives of our functionally illiterate veterans and become an important component of hypertension disease management and cardiovascular disease prevention in primary care clinics nationwide."

This study, to begin July 1st, is funded by the Pfizer Clear Communication Initiative for $150,000.

Opioid Analgesic Prescription among Osteoarthritis Patients

A recent study conducted by Durham VA researchers found "a relatively high prevalence of opioid analgesic prescription" among a group of 3,061 VA patients receiving treatment for osteoarthritis (OA). These results may indicate that opioids are gaining acceptance as a safe and effective treatment for chronic musculoskeletal pain, though some patients in this study were likely prescribed opioids for other types of conditions. Published in the most recent issue of *Journal of Pain and Palliative Care Pharmacotherapy**, researchers Kelli Dominick, Ph.D., and Hayden Bosworth, Ph.D., both of the Center for Health Services Research in Primary Care at the Durham VA Medical Center and the Duke University's Department of Medicine, Tara Dudley, M.Stat., of the of the Center for Health Services Research in Primary Care at the Durham VA Medical Center, and Sandra Waters, Ph.D., Lisa Campbell, Ph.D., and Francis Keefe, Ph.D., of Duke University Medical Center's Department of Psychiatry and Behavioral Sciences, concluded that, with the rise in the number of older adults, "opioid prescriptions may rise to unprecedented levels." The authors went on to say that the "merits and implications of increased opioid prescribing for OA should be considered within the broader context of other OA management," including non-opioid medications such as acetaminophen, nonselective and COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs), and non-pharmacological approaches such as exercise and pain coping skills training.

Opioid analgesics are recommended for OA patients who do not respond well to acetaminophens and NSAIDs. While they are found to be effective in reducing OA-related pain as well as improve patient sleep and mood, opioid analgesics are considered controversial due to concerns about toxicity, dependence and addiction. They also can have some adverse effects such as nausea, constipation, dizziness and increased risk of falls resulting in bone fractures.

Of particular note, the authors pointed out the unique advantages of VA databases for studying prescription medication use. Because medication co-payments are low and equal for all drug prescriptions, patients are motivated to obtain all of their medications through the VA health system. As a result, the VA pharmacy database reflects the patients' prescription drug regimens. Low co-payments also minimize the influence of economic and access-to-care issues. This gives a particular advantage in examining racial variations in care, which may contribute to disparities observed in some other health care systems. Finally, the VA pharmacy database provides detailed information about prescriptions, including days' supply and dosing.

The researchers further concluded that "further research is needed to determine whether increased prescribing of

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HSR&D
VA Medical Center (152)
508 Fulton Street
Durham, NC 27705

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opioids among patients with OA is occurring to the exclusion of other treatment approaches, or whether it coincides with wider approaches" as well as to continue efforts to ensure that "patients and physicians are well-educated about the benefits and risks of opioid prescription for chronic musculoskeletal pain."

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* Dominick KL, Bosworth HB, Dudley TK, Waters SJ, Campbell LC, Keefe FJ. "Patterns of opioid analgesic prescription among patients with osteoarthritis" *Journal of Pain and Palliative Care Pharmacotherapy* 2004;18(1):31-46.

Recent Faculty Publications

Forneris CA, **BUTTERFIELD MI**, **BOSWORTH HB**. "Physiological Arousal among Women Veterans with and without Posttraumatic Stress Disorder" *Military Medicine* 2004 (April); 169(4): 307-312.

DOMINICK KL, Ahern FM, Gold CH, Heller DA. "Health-Related Quality of Life and Health Service Among Older Adults with Osteoarthritis" *Arthritis & Rheumatism* 2004 (June 15); 51(3):326-331.

BOSWORTH HB, CALHOUN PS, STECHUCHAK KM, BUTTERFIELD MI. "Use of Psychiatric and Medical Health Care by Veterans With Severe Mental Illness" *Psychiatric Services* 2004 (June); 55(6):708-710.

Rao JK, **WEINBERGER M**, Andererson LA, Kroenke K. "Predicting Reports of Unmet Expectations among Rheumatology Patients" *Arthritis and Rheumatism* 2004 (April 15); 51(2):215-221.

Bundy BG, Berkoff MC, Ito KE, Rosenthal MS, **WEINBERGER M**. "Interpreting Subgroup Analysis: Is a School-Based Asthma Treatment Program's Effect Modified by Secondhnad Smoke Exposure?" *Archives of Pediatrics and Adolescent Medicine* 2004 (May): 158(5):469-71.

Research Update is published by the Health Services Research and Development Service, Department of Veterans Affairs Medical Center, Durham. For questions or comments contact Ed Cockrell, Administrative Officer, VAMC (152), 508 Fulton Street, Durham NC, 27705. Telephone: (919) 286-6936, Fax: (919) 416-5836. E-mail: COCKR001@mc.duke.edu Web Page: http://hsrd.durham.med.va.gov/ The Institute's mission is to provide quality information on issues regarding the organization, financing, and delivery of veterans' health care, and to build the epidemiological capacity of the Veterans Health Administration through the generation, synthesis, and dissemination of epidemiological information. The Institute also has a mission to educate health professionals through a spectrum of training grants in the techniques of health services and epidemiological research.